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January 4, 1995

(A)

Ms. Elizabeth Smith, Coordinator
TSCA Section 8(e)
Chemical Information Division
Office of Toxic Substances
Environmental Protection Agency
Washington, D.C. 20460

SANITIZED VERSION

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SUBJECT: Notification of Toxicity Results Which May be Considered Reportable Under TSCA 8(e)

COMPANY SANITIZED

Dear Ms. Smith:

Our company is currently developing a new insecticide at our Headquarters in Europe. This experimental compound is a soil insecticide which will be developed for use in corn and turf. It is presently used in very small quantities here in the U.S. for laboratory and field testing. We just received a summary of acute and subchronic toxicology information. It has an acute oral LD_{50} rate of 20 mg/kg and produces clinical signs of neurological effects (e.g. hyperactivity, tremors, twitches and ataxia) in rats, mice and dogs following subchronic dietary administration. A copy of the toxicity summary is attached. Given this information, we are reporting these preliminary findings under TSCA 8(e).

Since this insecticide is still at its early stage of development, only small quantities are handled with particular precautions.

If you have any questions concerning this submission, please do not hesitate to contact me directly.

Sincerely,

B. Volger

Bert Volger
Regulatory Affairs

attachments

5/24/95

BV:gdl:Smithtox

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TOXICOLOGY

[redacted]

SUBMISSION TO THE UNITED STATES EPA ON PROPOSALS FOR APPROPRIATE DOSE LEVELS FOR CHRONIC TOXICOLOGY IN RATS, MICE AND DOGS BASED ON PRECEDING SUB-CHRONIC, RANGE-FINDING AND REPEAT DOSE STUDIES

AUTHORS

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CONTENTS

APPENDICES

[redacted] : PROPOSED DOSE LEVELS FOR THE CHRONIC TOXICITY AND CARCINOGENICITY STUDIES

1 SUMMARY

[redacted] is a [redacted] primarily intended for use on corn root worm in the USA.

The compound has been evaluated in acute, subacute and 90-day repeat dose studies in rats, dogs and mice.

[redacted] shows a [redacted] profile with a high acute oral toxicity value and very low dermal value. [redacted] was not irritating to the skin or eye of rabbits and is not a sensitiser in guinea pigs.

Clinical signs, tremors, twitches, hyper-reactivity and/or death, are dose limiting in all species, with a steep dose response curve complicating the choice of the MTD in each species. Individual animal variation in sensitivity is seen. In the rat 28 day study 2 females dosed at 90 ppm died and in the 90 day study one female dosed at 100 ppm died of treatment-related effects, whereas other animals which showed lesser effects survived. Similarly in mice dosed at 480 ppm one female died. This probably reflects the known absorption variability with this class of compound.

We believe our proposals tread a fair balance in striking the MTD for a compound with such a steep dose response curve.

Our proposals are as follows :-

Dose	Species					
	Rat		Mouse		Dog	
	ppm	(mg/kg) *	ppm	(mg/kg) *	ppm	(mg/kg) *
High	100	(5)	300	(30)	220	(7.3)
Intermediate	20	(1)	30	(3)	36	(1.2)
Low	4	(0.2)	3	(0.3)	6	(0.2)

* Predicted achieved dose level of mg [redacted]/kg body weight/day over the dosing period.

The basis for this selection is shown in Section 2.

2 INTRODUCTION

[redacted] is a [redacted] insecticide intended for use on corn root worm and for white grubs in turf in the USA and in Europe as a soil insecticide.

This document presents the rationale with summary data to support the dose levels proposed for the combined chronic toxicity and oncogenicity study in the rat, the oncogenicity study in the mouse and the chronic toxicity study in the dog on this novel insecticide.

3 TOXICOLOGY

3.1 Acute toxicity

[redacted] was of high acute oral and very low acute dermal toxicity to rodents. It was not irritant to rabbit skin or eye and was not a sensitiser in the guinea pig (Magnusson & Kligman test).

Table 1

Summary of acute toxicity and classification

Route	Species	Sex	LD_{50} mg/kg (with 95% confidence limits)	Classification	
				OECD	EPA
Oral	Rat	Combined	20 (11-29)	Labelling with risk phrase R28	Toxic category I
Dermal	Rat	Combined	>2000	Labelling not indicated	Toxic category III
Skin irritancy	Rabbit	F	Negative	Labelling not indicated	Toxic category IV
Eye irritancy	Rabbit	F	Negative	Labelling not indicated	Toxic category III
Skin sensitisation	Guinea pig	F	Negative	Labelling not indicated	-

3.2 Subchronic toxicity

The subchronic toxicity of [redacted] has been assessed in the rat, mouse and dog. Summaries of the findings for each of the studies conducted in these species are presented below.

The studies are presented in chronological sequence, certain studies having had to be repeated to more clearly define tolerated dose levels and dose response.

3.2.1 Rat 28-day range-finding study (Appendix 1)

Groups of six male and six female CRL:CD(SD)BR rats received [redacted] by dietary administration at levels of 0, 10, 30, 90 or 150 ppm for four weeks. The achieved intakes were 1.0/1.0, 2.9/2.8, 9.0/8.2 and 15.0/- in males/females respectively at each of 10, 30, 90 and 150 ppm.

At 150 ppm, all females were killed prematurely or found dead within 3 days of treatment. Increased sensitivity to noise, tremors, startling and/or clonic contractions were noted at this dose level. Chromorhinorrhea was also noted in some females. Slightly reduced body weight gain, in line with slightly reduced food consumption during the first week of treatment was noted.

At 90 ppm, 2 females were found dead after 20 days of treatment, some females also showed increased sensitivity to noise. A very slight palatability affect was noted at both 90 and 30 ppm.

No other significant findings were detected and the no adverse effect level was considered to be 30 ppm.

3.2.2 Rat 14 day range-finding study (Appendix 2)

Groups of five male and five female CRL:CD(SD)BR rats were treated with [redacted] in the diet for 14 consecutive days. Males received concentrations of 0, 110 and 220 ppm (equivalent to 13.7 and 29.1 mg/kg/day respectively) and females received concentrations of 0 and 60 ppm (equivalent to 7.8 mg/kg/day).

At 220 ppm, hyper-reactive behaviour was seen in all males between days 2 and 15, with tremors and/or twitches observed in all animals from days 2 to 4. Body weight gain was reduced by 8% in males compared to controls during the first week of the study.

At 110 ppm, hyper-reactive behaviour was seen in all males between days 2 and 7. Body weight gain was reduced by 6% in males compared to controls over the course of the study.

At 60 ppm, all females exhibited hyper-reactive behaviour on day 2 and between days 13 and 15. At 60 ppm, body weight gain was reduced by 14% in females compared to controls during the first week, and by 6% over the course of the study.

There was no apparent effect of treatment on food consumption at any dose level.

There was no apparent effect on the palatability of the test material to rats at dose levels up to 220 ppm for males and 60 ppm for females.

Dose levels of between 110 and 220 ppm (equivalent to 13.7 to 29.1 mg/kg/day) for males and 60 ppm (equivalent to 7.8 mg/kg/day) for females appeared to approximate to the maximum tolerated dose (MTD) at this duration of dosing, based on reduced body weight gain.

3.2.3 **Rat 90-day repeat dose study (Appendix 3)**

Groups of 10 male and 10 female CRL:CD(SD)BR rats were fed diet containing 0, 8, 25, 50 or 100 ppm (equivalent to 0, 0.6, 1.9, 3.9 or 7.5 mg/kg/day respectively) for 13 weeks. A further 10 males and 10 females (regression animals), were fed either 0, 50 or 100 ppm for 13 weeks, and were then maintained on control diet for 4 weeks to examine the reversibility of any effects seen.

At 100 ppm, one female rat died during week 5 after exhibiting signs of severe hyper-reactivity and twitches. Intermittent hyper-reactive behaviour was seen in all other females. Body weight gain was reduced in males (by 11% compared to controls) after 4 weeks of treatment and in females (by 17%) during week 1. There was an apparent reduction in water consumption by up to 25% in both males and females. Liver weights relative to body weights were statistically significantly increased (by 10% compared to controls) in female rats. The number of renal tubular cytoplasmic inclusions was increased in males only. All effects of treatment were found to be reversible following 4 weeks off-dose.

At 50 ppm, body weight gain was reduced in males by 7% compared to controls over the course of the study.

No treatment-related effects were seen at 8 or 25 ppm.

The no observed effect level (NOEL) for the combined sexes was 25 ppm, equivalent to a daily intake of 1.9 mg/kg/day.

50 ppm, equivalent to a daily intake of 3.9 mg/kg/day, was considered to be the no observed adverse effect level (NOAEL).

3.2.4 **Mouse 28-day range-finding study (first study) (Appendix 4)**

Dose levels of 0, 10, 30, 90 or 120 ppm were administered to groups of six male and six female CRL:CD-1(ICR)BR mice for four weeks. The achieved intakes in males/females were 2.0/2.6, 5.9/8.3, 16.7/24.0 and 23.9/32.9 for males and females respectively.

There was no effect on body weight and food consumption. No treatment-related findings were identified in haematology or organ weights and the macroscopic/microscopic findings were those commonly recorded in this species and were not treatment-related.

The no effect level was at least 120 ppm.

3.2.5 **Mouse 28-day range-finding study (second study) (Appendix 5)**

Two groups of 6 male and 6 female CRL:CD-1(ICR)BR mice received [redacted] by dietary admixture, a similar sized control group received untreated diet. The study was extended by 4 weeks over the originally planned 4 week dosing period.

In the first treated group, males and females received 240 ppm for 4 weeks and then 720 ppm for the remaining 4 weeks.

In the second treated group, males received 480 ppm for the first 4 weeks and then 960 ppm for the remaining 4 weeks; females received 480 ppm throughout the 8 week treatment period.

The achieved test material intakes at each of 240, 480, 720, 960 ppm (males only) were 47.7/73.4, 88.1/111.9, 125.4/164.7, 155/0 mg/kg/day in males/females respectively.

One male was found dead at 960 ppm, four females at 720 ppm were found dead or killed in extremis and one female at 480 ppm was found dead.

Tremors were noted in males when treated at 960 ppm. Tremors, startling, and dyspnoea were noted in females when treated at 720 ppm. Reduced body weight gain was detected in males at 720 ppm and body weight loss in males whilst at 960 ppm. Increased liver weights and slight to moderate hepatocyte hypertrophy were seen in all animals.

3.2.6 **Mouse 14-day range-finding study (Appendix 6)**

Groups of five male and five female CRL:CD-1(ICR)BR mice were treated with [redacted] in the diet for 14 consecutive days at concentrations of 0 and 400 ppm (equivalent to 86 and 105 mg/kg/day for males and females respectively).

At 400 ppm, tremors were seen in a single male on day 2 and slightly increased activity in one female on day 11 only. Body weight gain was increased in both males (by 16%) and females (by 33%) compared to control animals. Food consumption was generally increased in treated males (by 3%) and females (by 11%) compared to their respective controls. This did not appear to be due to any increased scatter in treated groups.

There was no effect on the palatability of the test material to mice at 400 ppm (equivalent to 96 mg/kg/day for males and females combined).

3.2.7 **Mouse 90-day repeat dose study (Appendix 7)**

Groups of 10 male and 10 female CRL:CD-1(ICR)BR mice were fed diet containing 0, 4, 40, 120, 240 or 480 ppm (equivalent to 0, 0.75, 7.5, 23, 46 or 91 mg/kg/day respectively) for 13 weeks.

At 480 ppm, there were no untoward clinical signs. Body weight gain was reduced by 10-13% in males compared to controls between weeks 8 and 12. A mild reduction in total white blood cells, lymphocytes, monocytes and neutrophils, together with a mild but significant increase in creatine kinase, were seen in female mice only. Liver weights relative to body weight were significantly increased in males and females (by 19% and 14% respectively) compared to controls. Centrilobular hepatocyte enlargement in the livers of males and females, and focal degeneration of the panniculus carnosus muscle and cellulitis in males only were observed histopathologically.

At 240 ppm, body weight gain was reduced by 10-15% in males compared to controls between weeks 7 and 13. A mild reduction in total white blood cells, lymphocytes and monocytes, together with a mild but significant increase in creatine kinase, were seen in female mice only. Liver weights relative to body weight were significantly increased in males and females (by 12% and 18% respectively) compared to controls. Focal degeneration (mild to moderate) of the panniculus carnosus muscle in males only was observed histopathologically.

At 120 ppm, focal degeneration of the panniculus carnosus muscle in males only was observed.

No treatment-related effects were seen at 40 ppm or below.

The no observed effect level (NOEL) for the combined sexes was 40 ppm, equivalent to a daily intake of 7.5 mg/kg/day.

The no observed adverse effect level (NOAEL) was 120 ppm, equivalent to a daily intake of 23 mg/kg/day.

3.2.8 Dog 28-day range-finding study (Appendix 8)

Groups of 1 male and 1 female Beagle dog were initially dosed at 5, 20, 60 and 120 ppm by dietary admixture. The dose levels were then increased and the study extended due to the absence of evident toxicity according to the table detailed overleaf. Achieved intakes in mg/kg/day are indicated over each time period.

Group	Dose (ppm)		Achieved intakes (mg/kg/day)	
			Males	Females
1	5	(1 week)	0.15	0.17
	230	(4 weeks)	7.22	8.08
2	20	(2 weeks)	0.54	0.52
	460	(4 weeks)	12.47	7.99
3	60	(2 weeks)	1.47	1.40
	460	(4 weeks)	12.47	7.99
4	120	(4 weeks)	3.55	2.85

At 460 ppm, tremors were noted in all animals, ataxia in 2/2 males, and vomiting in all dogs (for the first three days). Reduced food consumption and body weight loss (11-17%) were also noted in all animals. Increased levels of fibrinogen, alkaline phosphatase and cholesterol were also noted in these animals.

At 230 ppm, body weight loss (7-9%) was noted in both animals.

No other effects were noted and the no effect level was, therefore 120 ppm.

3.2.9 **Dog 11-day range-finding study (Appendix 9)**

One male and 1 female beagle dog were initially dosed at 250 ppm RU 58753 in the diet for 4 days, followed by 200 ppm for a further 7 days.

On day 1 both animals ate a full 400 g ration and the achieved intake was, therefore, c. 10 mg/kg body weight. The female showed tremors and following 3 further days administration at this level both animals were losing weight with food consumption oscillating between c. 100 and 400 g on alternate days.

On day 5 the dose level was reduced to 200 ppm. No further clinical signs were seen and food consumption in both dogs returned to 400 g/day, thus giving an achieved intake of c. 8 mg/kg/day.

250 ppm was not well tolerated whilst a reduction to 200 ppm (c. 8 mg/kg/day) allowed tolerance over the remainder of the study.

3.2.10 **Dog 90-day repeat dose study (Appendix 10)**

Groups of 4 male and 4 female beagle dogs were treated by dietary admixture at 0, 16.5, 55 or 220 ppm (equating to 0, 0.6, 2.0 and 7.9 mg/kg/day for the combined sexes) for at least 92 consecutive days. An additional two male and two female dogs were maintained at 0 or 220 ppm for 92 days and were then kept off-dose for 4 weeks to assess the reversibility of noted effects. Control animals received plain diet.

At 220 ppm, tremors were seen in 5/6 male and 6/6 females during the first week of treatment and then occasionally to week 7 in males and the end of treatment in females. Vomiting was noted in 3/6 females in week 1 only. Body weight gain was reduced by approximately 7% in males over the course of the study. Food consumption was very slightly reduced in both sexes in the first week of treatment. A mild but statistically significant increase in alkaline phosphatase was noted in females at weeks 6 and 13, this response had returned to normal following the regression period.

No treatment-related effects were noted at the intermediate (55 ppm) or low (16.5 ppm) dose level.

The no observed effect level (NOEL) for both sexes was 55 ppm technical [redacted], equating to 2.0 mg/kg/day for the combined sexes.

4 DOSE LEVEL PROPOSALS BASED ON SUBACUTE AND SUBCHRONIC RANGE-FINDING STUDIES

The low dose levels have been selected for each species on the basis of the following criteria. This product is expected to have nil residues in the in-use situation as it is directly applied to the soil and has minimal foliar uptake. On this basis the low dose levels have been set at levels predicted to provide clear no-effect levels and to be close to the limit of detection in test animal diet without compromising reproducibility and homogeneity of mixing.

The high dose levels are based on the estimated maximum tolerated dose predicted from the 90 day repeat dose studies.

The intermediate dose approximates to the midpoint of high and low doses in each case and also takes into account the predicted no effect levels from the 90 day studies.

The rationale for the selection of dose levels for each of the studies is presented in detail as follows :-

i) Combined rat chronic and oncogenicity study - Section 5
ii) Mouse oncogenicity study - Section 6
iii) Dog chronic toxicity study - Section 7

A summary of the proposed dose levels (Table 2) is presented below.

Table 2

Proposed dose levels for the chronic toxicity and carcinogenicity studies

Dose	Species					
	Rat		Mouse		Dog	
	ppm	*(mg/kg)	ppm	*(mg/kg)	ppm	*(mg/kg)
High	100	(5)	300	(30)	220	(7.3)
Intermediate	20	(1)	30	(3)	36	(1.2)
Low	4	(0.2)	3	(0.3)	6	(0.2)

* Predicted achieved dose level of mg [redacted]/kg body weight/day over the dosing period.

5 DOSE LEVELS FOR THE RAT COMBINED CHRONIC TOXICITY AND CARCINOGENICITY STUDY ON [redacted] (STUDY NUMBER TOX 94359)

Dose levels of 0, 4, 20 and 100 ppm have been selected for the combined rat chronic toxicity and carcinogenicity study on the following basis :-

a) 100 ppm, as a high dose level, is predicted to equate to approximately 5 mg/kg/day over the chronic period. This dose level, in the subchronic study, resulted in the death of one female during week 5, after exhibiting signs of severe hyper-reactivity and twitches. (In the 28-day study, two females died following treatment at 90 ppm.) Intermittent hyper-reactivity was seen in all other females in the subchronic study. Body weight gain was reduced in males (by 11% compared to controls after 4 weeks) and females (by 7% compared to controls in week 1 only). Relative liver weights were increased in females (by 10% compared to controls) and there was an increase in the number of renal hyalin droplets in males only. All effects were shown to be reversible. Due to the steep dose response curve of the test material (only a slight body weight effect was seen at 50 ppm) and the knowledge from the subacute study that a higher dose level would almost certainly result in an unacceptable level of female mortality, it is considered that 100 ppm should be employed as a high dose level: the effects seen initially during the 90 day study will most probably be repeated (with a lessening in severity as the study progresses).

b) 4 ppm, as a low dose level, is predicted to equate to approximately 0.2 mg/kg/day. This dose level is expected to be a clear no effect level and provides satisfactory margins of safety in the predicted nil residue situation. It also equates to the low dose level in the mouse and dog chronic studies.

c) 20 ppm, as an intermediate dose level is predicted to equate to approximately 1 mg/kg/day. This dose level provides a factor of 5 between high and low dose levels and, on the basis of the subchronic study, is predicted to provide a clear no effect level.

6 DOSE LEVELS FOR THE MOUSE ONCOGENICITY STUDY ON [redacted] (STUDY NUMBER TOX 94360)

Dose levels of 0, 3, 30 and 300 ppm have been selected for the mouse oncogenicity study on the following basis :-

a) 300 ppm, as a high dose level, is predicted to equate to approximately 30 mg/kg/day. It is predicted to be the MTD on the basis of the results of the 90-day repeat dose study in the mouse and in an earlier study where deaths were observed at 480 ppm and above.

In the 90-day mouse study, dose levels of 240 and 480 ppm resulted in reduced body weight gain in males (during weeks 7 to 13), mild but significant reductions in white blood cell parameters and a mild but significant increase in creatine kinase in females only, increased relative liver weights in both males and females of up to 19% compared to controls, and centrilobular hepatocyte enlargement at the high dose only. The chemical pathology and histopathology findings occurred with a shallow dose response in this study, particularly since the finding of focal degeneration (minimal-moderate) of the panniculus carnosus muscle, in male mice only, was seen at 120, 240 and 480 ppm. It is possible that this was caused by increased fighting early in the study, since these findings are indications of earlier damage through the skin which is repairing. There was no evidence of such effects in-life, although animals were group housed. A dose level of 300 ppm, between the two main effect levels, was therefore selected since this was estimated to equate to the MTD over the chronic period.

b) 3 ppm, as a low dose level, is predicted to equate to approximately 0.3 mg/kg/day. This dose level is expected to be a clear no effect level and provides satisfactory margins of safety in the predicted nil residue situation. It also equates approximately to the low dose levels in the rat and dog chronic studies.

c) 30 ppm, as an intermediate dose level is predicted to equate to 3 mg/kg/day. This dose level provides a factor of 10 between high and low dose levels and, on the basis of the subchronic study, is predicted to provide a clear no effect level.

7 DOSE LEVELS FOR THE DOG CHRONIC TOXICITY STUDY ON [redacted] (STUDY NUMBER TOX 94358)

Dose levels of 0, 6, 36 and 220 ppm have been selected for the chronic toxicity study in the dog on the following basis :-

a) 220 ppm, as a high dose level, is predicted to equate to approximately 7.3 mg/kg/day over the chronic period. This dose level in the subchronic study caused tremors in 11/12 dogs and vomiting in 3/6 females during the first week of treatment. Other effects noted included increased alkaline phosphatase in females at weeks 6 and 13 and a decrease in male body weight gain of 7% over the course of the study. Due to the steep dose response curve of the test material it is considered that a higher dose level could not be tolerated during the initial months of the study. It is expected that the overt signs of toxicity at this dose level will lessen during the course of the study.

b) 6 ppm, as a low dose level, is predicted to equate to 0.2 mg/kg/day. This dose level is expected to be a clear no effect level and provides satisfactory margins of safety in the predicted nil residue situation.

c) 36 ppm, as an intermediate dose level is predicted to equate to 1.2 mg/kg/day. This dose level provides a factor of 6 between high and low dose levels and, on the basis of the subchronic study, is predicted to provide a clear no effect level.

APPENDIX 1

[redacted] : RAT 28-DAY RANGE-FINDING STUDY

	Males					Females				
Dose level (ppm)	0	10	30	90	150	0	10	30	90	150
Achieved intake (mg/kg/day)	-	1.0	2.9	9.0	15.0	-	1.0	2.8	8.2	-
Mortality	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	2/6	6/6
Clinical signs	-	NE	NE	NE	Hyperreactivity, tremors, chronic contractions	-	NE	NE	Hyperreactivity	Hyperreactivity, tremors, chronic contractions, chromorhinorrhea
Body weight*	-	NE	NE	NE	↓gain	NE	NE	↓gain	↓gain	-
Food consumption*	-	NE	NE	NE	↓	NE	NE	↓	↓	-
Haematology	-	NE	NE	NE	NE	-	NE	NE	NE	NE
Biochemistry	-	NE	NE	NE	NE	-	NE	NE	NE	NE
Urinalysis	-	NE	NE	NE	NE	-	NE	NE	NE	NE
Organ weights	-	NE	NE	NE	NE	-	NE	NE	NE	NE
Macroscopic and microscopic pathology	-	NE	NE	NE	NE	-	NE	NE	NE	NE

Key :

NE = No treatment-related effect
↓ = Decreased
* = Effects seen during first week only and considered to be palatability effect

APPENDIX 2

[redacted] : RAT 14 DAY RANGE-FINDING STUDY

	Males	Females
Dose level (ppm)	110 and 220	60
Achieved intake (mg/kg/day)	13.7 and 29.1	7.8
Mortality	-	-
Clinical signs	Hyperreactivity (110 and 220), tremors (220), twitches (220)	Hyperreactivity (60)
Food consumption	NE	NE
Body weight gain	↓ (110 and 220)	↓ (60)

Key :

NE = No treatment-related effect
↓ = Reduced

APPENDIX 3

[redacted] : RAT 90-DAY REPEAT DOSE STUDY

	Males					Females				
Dose level (ppm)	**0**	**8**	**25**	**50**	**100**	**0**	**8**	**25**	**50**	**100**
Achieved intake (mg/kg/day)	**0**	**0.6**	**1.8**	**3.6**	**7.0**	**0**	**0.6**	**2.0**	**4.2**	**8.0**
Mortality	**0/20**	**0/10**	**0/10**	**0/20**	**0/20**	**0/10**	**0/10**	**0/10**	**0/10**	**1/10**
Clinical signs **Hyperreactivity** **Twitches**	**0/20** **0/20**	**0/10** **0/10**	**0/10** **0/10**	**0/20** **0/20**	**0/20** **0/20**	**0/20** **0/20**	**0/10** **0/10**	**0/10** **0/10**	**0/20** **0/20**	**20/20** **1/20**
Body weight gain	**-**	**NE**	**NE**	**↓(7%)**	**↓(11%) (after 4 weeks)**	**-**	**NE**	**NE**	**NE**	**↓(17%) (week 1 only)**
Food consumption	**-**	**NE**	**NE**	**NE**	**NE**	**-**	**NE**	**NE**	**NE**	**NE**
Water consumption	**-**	**NE**	**NE**	**NE**	**↓**	**-**	**NE**	**NE**	**NE**	**Apparent ↓**
Haematology	**-**	**NE**	**NE**	**NE**	**NE**	**-**	**NE**	**NE**	**NE**	**NE**
Biochemistry	**-**	**NE**	**NE**	**NE**	**NE**	**-**	**NE**	**NE**	**NE**	**NE**
Urinalysis	**-**	**NE**	**NE**	**NE**	**NE**	**-**	**NE**	**NE**	**NE**	**NE**
Ophthalmoscopy	**-**	**NE**	**NE**	**NE**	**NE**	**-**	**NE**	**NE**	**NE**	**NE**
Relative liver weights - 13 wks **- Regression**	**-** **-**	**NE** **-**	**NE** **-**	**NE** **NE**	**NE** **NE**	**-** **-**	**NE** **-**	**NE** **-**	**NE** **NE**	**↑10%** **NE**
Histopathology - Renal hyaline droplets	**-**	**NE**	**NE**	**NE**	**↑**	**-**	**NE**	**NE**	**NE**	**NE**

Key :

NE = No treatment-related effect
↑ = Increase (with associated % compared to controls)
↓ = Decrease (with associated % compared to controls)

APPENDIX 4

[redacted] : MOUSE 28-DAY RANGE-FINDING (FIRST STUDY)

	Males					Females				
Dose level (ppm)	0	10	30	90	120	0	10	30	90	120
Achieved intake (mg/kg/day)	-	2.0	5.9	16.7	23.9	-	2.6	8.3	24.0	32.9
Mortality	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	1/6
Clinical signs	-	NE	NE	NE	NE	-	NE	NE	NE	NE
Body weight	-	NE	NE	NE	NE	-	NE	NE	NE	NE
Food consumption	-	NE	NE	NE	NE	-	NE	NE	NE	NE
Haematology	-	NE	NE	NE	NE	-	NE	NE	NE	NE
Organ weights	-	NE	NE	NE	NE	-	NE	NE	NE	NE
Macroscopic/ microscopic findings	-	NE	NE	NE	NE	-	NE	NE	NE	NE

Key :

NE = No treatment-related effect

APPENDIX 5

[redacted] : MOUSE 28-DAY RANGE-FINDING STUDY (SECOND STUDY)

	Males			Females		
Dose level (ppm)	0	240/720	480/960	0	240/720	480
Achieved intake (mg/kg/day)	-	47.7/125.4	88.1/155.0	-	73.4/164.7	111.9
Mortality	0/6	0/6	1/6 (960)	0/6	4/6 (720)	1/6
Clinical signs	-	NE	Tremors (960)	-	Tremors, startling, dyspnoea (720)	NE
Body weight	-	↑gain (720)	Loss (960)	-	NE	NE
Food consumption	-	NE	NE	-	NE	NE
Haematology	-	NE	NE	-	NE	NE
Organ weights	-	↑Liver	↑Liver	-	↑Liver	↑Liver
Macroscopic findings	-	NE	NE	-	NE	NE
Microscopic findings - Liver	-	Hepatocellular hypertrophy		-	Hepatocellular hypertrophy	

Key :

NE = No treatment-related effect
↑ = Increase
↓ = Decrease

APPENDIX 6

[redacted] : MOUSE 14-DAY RANGE-FINDING STUDY

	Males	Females
Dose level (ppm)	400	400
Achieved intake (mg/kg/day)	86	105
Mortality	-	-
Clinical signs	Tremors	Increased activity
Food consumption	↑	↑
Body weight gain	↑	↑

Key :

↑ = Increased

APPENDIX 7

[redacted] : MOUSE 90-DAY REPEAT DOSE STUDY

	Males						Females					
Dose level (ppm)	0	4	40	120	240	480	0	4	40	120	240	480
Achieved intake (mg/kg/day)	0	0.63	6.0	18	40	79	0	0.86	8.9	28	53	102
Mortality	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Clinical signs	-	NE	NE	NE	NE	NE	-	NE	NE	NE	NE	NE
Body weight gain	-	NE	NE	NE	↓(15%) (weeks 7-13)	↓(13%) (weeks 8-12)	-	NE	NE	NE	NE	NE
Food consumption	-	NE	NE	NE	NE	NE	-	NE	NE	NE	NE	↓(sl)
Haematology												
Total WBC	-	NE	NE	NE	NE	NE	-	NE	NE	NE	↓mild*	↓mild*
Lymphocytes	-	NE	NE	NE	NE	NE	-	NE	NE	NE	↓mild*	↓mild*
Monocytes	-	NE	NE	NE	NE	NE	-	NE	NE	NE	↓mild*	↓mild*
Neutrophils	-	NE	NE	NE	NE	NE	-	NE	NE	NE	NE	↓mild*
Biochemistry												
Creatine kinase	-	NE	NE	NE	NE	NE	-	NE	NE	NE	↑mild*	↑mild*
Relative liver weight	-	NE	NE	NE	↑(12%)	↑(19%)	-	NE	NE	NE	↑(18%)	↑(14%)
Histopathology												
Centrilobular hepatocyte enlargement	0/10	0/10	0/10	0/10	0/10	9/10 min-mod	0/10	0/10	0/10	0/10	0/10	2/10 min-mod
Cellulitis	0/10	0/10	0/10	0/10	0/10	4/10	0/10	0/10	0/10	0/10	0/10	0/10
Focal degeneration of panniculus carnosus	0/10	0/10	0/10	2/10	2/10	7/10 min-mod	0/10	0/10	0/10	0/10	0/10	0/10

Key :

NE = No treatment-related effect
↑ = Increase (with associated % of controls)
↓ = Decrease (with associated % of controls)
* = Statistically significant effect
Min = Minimal
Mod = Moderate

APPENDIX 8

[redacted] : DOG 28-DAY RANGE-FINDING STUDY

	Males				Females			
Dose level (ppm)	5/230	20/460	60/460	120	5/230	20/460	60/460	120
Achieved intake (mg/kg/day)	0.15/ 7.22	0.54/ 12.47	1.7/ 12.47	3.55	0.17/ 8.08	0.52/ 7.99	1.4/ 7.99	2.85
Mortality	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
Clinical signs		(460)	(460)				(460)	
Tremors	NE	1/1	1/1	NE	NE	NE	1/1	NE
Vomiting	NE	1/1	1/1	NE	NE	NE	1/1	NE
Ataxia	NE	1/1	1/1	NE	NE	NE	NE	NE
Body weight	Loss (230)	Loss (460)	Loss (460)	NE	Loss (230)	Loss (460)	Loss (460)	NE
Food consumption	NE	↓ (460)	↓ (460)	NE	NE	↓ (460)	↓ (460)	NE
Haematology	NE	NE	NE	NE	NE	NE	NE	NE
Biochemistry								
Fibrinogen	NE	↑ (460)	↑ (460)	NE	NE	↑ (460)	↑ (460)	NE
Alkaline phosphatase	NE	↑ (460)	↑ (460)	NE	NE	NE	NE	NE
Cholesterol	NE	↑ (460)	↑ (460)	NE	NE	↑ (460)	↑ (460)	NE

Key :

↑ = Increased
↓ = Decreased
NE = No treatment-related effect

APPENDIX 9

[redacted] : DOG 10-DAY RANGE-FINDING STUDY

	Males	Females
Dose level (ppm)	250 for 4 days 200 for 7 days	250 for 4 days 200 for 7 days
Achieved intake (mg/kg/day)	8 (200 ppm)	8 (200 ppm)
Mortality	-	-
Clinical signs	NE	Tremors (250)
Food consumption	↓ (250)	↓ (250)
Body weight	Loss (250)	Loss (250)
Organ weights	NE	NE
Macroscopic findings	NE	NE

Key :

NE = No treatment-related effect
↓ = Reduced

APPENDIX 10

[redacted] : DOG 90-DAY REPEAT DOSE STUDY

	Males				Females			
Dose level (ppm)	0	16.5	55	220	0	16.5	55	220
Achieved intake (mg/kg/day)	0.6, 2.0 and 7.9 for combined sexes at 16.5, 55 and 220 ppm							
Mortality	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Clinical signs Tremors Vomiting	 0/6 0/6	 0/6 0/6	 0/6 0/6	 5/6 0/6	 0/6 0/6	 0/6 0/6	 0/6 0/6	 6/6 3/6
Body weight	-	NE	NE	↓gain 7%	-	NE	NE	NE
Food consumption	-	NE	NE	Slight ↓ wk 1 only	-	NE	NE	Slight ↓ wk 1 only
Haematology	-	NE	NE	NE	-	NE	NE	NE
Biochemistry	-	NE	NE	NE	-	NE	NE	↑Alkaline phosphatase wk 6, 13
Regression	-	NE	NE	NE	-	NE	NE	NE
Ophthalmoscopy	-	NE	NE	NE	-	NE	NE	NE
Electrocardiography	-	NE	NE	NE	-	NE	NE	NE
Organ weight	-	NE	NE	NE	-	NE	NE	NE
Macroscopic & microscopic pathology	-	NE	NE	NE	-	NE	NE	NE

Key :

NE = No treatment-related effect
↓ = Decrease

EPSR/GH/LSS/NK
SED\0529.LSS
9 December 1994

Triage of 8(e) Submissions

Date sent to triage: _____ NON-CAP CAP

Submission number: 13304A TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: 0 (1) 2 **pages** 1 **pages** _____

Notes:

Contractor reviewer : JW **Date:** 1/24/96

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # BEHQ: 0195 - 13304 (5) SEQ. A

TYPE: INT SUPP FLWP

SUBMITTER NAME: AgrEvo USA Company

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
0639 REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF MARKET RESTRICTIONS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 01/04/95 OTS DATE: 01/06/95 CSRAD DATE: 05/24/95

CHEMICAL NAME: Confidant

CASE Confidant

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF E /V CONTAM	01 02 04
0223	RESPONSE REQUST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PRODUSE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:
	YES	YES (DROP/REFER)	RAT	LOW
CAS SR	NO	NO (CONTINUE)	MUS DOG GP RBT	MED
	IN TERMINI	REFER		HIGH

USE: Expor. Soil insecticide / corn root worm

PRODUCTION:

SUMMARY: Non-CAP The test material was evaluated in acute, subacute and 90-day studies in rats, dogs and mice. Treatment-related clinical signs of neurological effects which included hyperactivity, tremors, twitches and ataxia in the test animals. The NOAEL's for the 90 day studies were 3.9, 2.0, 23.0 mg/kg/day, respectively in rats, dogs and mice.

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # 8EHQ- 0195 - 13304 (3) SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: AgrEvo USA Company

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER EXPOSURE
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 01/04/95 OTS DATE: 01/06/95 CSRAD DATE: 05/24/95

CHEMICAL NAME: Confident

CAS# Confident

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
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0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
(0209)	NEURO (ANIMAL)	(01) 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
(0212)	ACUTE TOX. (ANIMAL)	(01) 02 04
(0213)	SUB ACUTE TOX (ANIMAL)	(01) 02 04
(0214)	SUB CHRONIC TOX (ANIMAL)	(01) 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF E IV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
(0224)	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
(0228)	ALLERG (ANIMAL)	(01) 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
(0248)	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

[redacted]

TRIAGE DATA:

NON-CBI INVENTORY
YES
CAS SR NO
(IN TERMINI)
UNKNOWN Non-CAP

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER

SPECIES
RAT
mus
DOG
GP
RBT

TOXICOLOGICAL CONCERN:
(LOW) Acute Dermal Toxicity, Dermal Irritation, Ocular Irritation, Subacute Dietary Toxicity
(MED) Subacute Dietary Toxicity
(HIGH) Acute Oral Toxicity

USE: EXPOS SOIL INSECTICIDE/ corn root worm

PRODUCTION:

13304A

H

Acute oral toxicity is of high concern based on a calculated LD_{50} of 20 mg/kg in rats.

M H

high

Subacute dietary toxicity is of ~~medium~~ concern based on lethality in rats (6/sex/dose) exposed to diets containing 0, 10, 30, 90 or 150 ppm (equivalent to 0, 1/1, 2.9/2.8, 9.0/8.2, and 15.0 mg/kg/day in males/females, respectively) for 4 weeks. Mortality and corresponding doses (ppm) were 0/12 (10, 30), 2/12 (90) and 6/12 (150). Clinical signs included hyperactivity (≥90), tremors and chronic contractions (150).

M

Subacute dietary toxicity is of medium concern based on the results of 2 studies in mice. Mice (6/sex/dose) were exposed for 28 days to doses of 0, 10, 30, 90 or 120 ppm (equivalent to 0, 2.0/2.6, 5.9/8.3, 16.7/24.0 and 23.9/32.9 mg/kg/day for males/females, respectively). There was 1 death in the females at the high dose. The NOEL was 120 ppm. In the second study, mice (6/sex/dose) were exposed to 240 ppm for 4 weeks, and 720 ppm for 4 more weeks; a second group (males only) was exposed to 480 ppm for 4 weeks, and 960 ppm for 4 more weeks; a group of females was exposed to 480 ppm for 8 weeks. The ppm equivalents (mg/kg/day) for males/females were: 240 (47.7/73.4), 480 (88.1/111.9), 720 (125.4/164.7) and 960 (155.0). Mortality and corresponding doses (ppm) were 0/6 (240/720, males), 1/6 (480/960, males; 480, females) and 4/6 (240/720, females). Clinical signs included tremors (720, females; 960, males) and dyspnea (720, females); histopathology included hepatocellular hypertrophy (all doses).

M

Subacute dietary toxicity is of medium concern based on neurotoxicity in dogs (1/sex) exposed to 250 ppm (10 mg/kg/day) for 4 days and 200 ppm (8 mg/kg/day) for 7 more days. Tremors were observed in the female dog at 250 ppm.

L

Acute dermal toxicity is of low concern based on an estimated LD_{50} > 2000 mg/kg in rats.

L

Dermal irritation is of low concern based on no irritation in rabbits.

L

Ocular irritation is of low concern based on no irritation in rabbits.

L

Dermal sensitization is of low concern based on no evidence of sensitization in guinea pigs.

~~L~~ M

medium

Subacute dietary toxicity is of ~~low~~ concern based on no mortality in rats exposed to 60 ppm (females, equivalent to 7.8 mg/kg/day), 110 and 220 ppm (males, equivalent to 13.7 and 29.1 mg/kg/day) for 14 days. Clinical signs included hyperactivity (all doses), tremors and twitches (220 ppm).

L

Subacute dietary toxicity is of low concern based on no mortality in mice exposed to 400 ppm for 14 days (equivalent to 86 and 105 mg/kg/day in males and females, respectively). Clinical signs included tremors (males) and hyperactivity (females).